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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,760	06/22/2000	Martha K. Newell	I0277/7009 HCL	8006

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/599,760	NEWELL, MARTHA K.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *60-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *60-62* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 12-27-04.

Claims 60-62 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12-27-04 has been entered.

Response to Arguments and Amendments

Any rejections not repeated in this Office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 60-62 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 60, lines 3-4, it is unclear whether the UCP antibody is the same entity as the UCP inhibitor and the lysosomal targeted binding peptide. Appropriate clarification is requested.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to a method for regulating lysosomal pH by modifying lysosomal UCP activity comprising contacting a cell with a lysosomal UCP inhibitor that is a UCP antibody.

The state of the prior art and the predictability or unpredictability of the art. The following references are cited herein to illustrate that the field of in vivo polypeptide and/or antibody delivery is still in its infancy and many hurdles remain before it is enabled for in vivo, therapeutic applications. Stayton et al teach that key delivery challenges remain before many biomolecule therapeutics reach the clinic, with the biggest barriers being effective drug targeting to specific tissues and cells, and subsequent intracellular delivery to appropriate cellular compartments (*see* Stayton, P.

et al, J. Controlled Release, 65: 203-220, 2000 at the abstract on p. 203). Stayton et al stress that the intracellular delivery issue is a major challenge to achieving clinical efficacy: "Targeting to appropriate cells is not sufficient for therapy involving drugs which act intracellularly... The efficacy of several important protein and DNA therapeutics is subsequently limited by nonproductive intracellular trafficking..." (*see* Stayton et al at p. 204, right column). In speaking directly to in vivo success using antibodies, Stayton et al stress that "...several important hurdles to their productive and effective use in cancer treatments have been identified... A principle problem with the engineered fragments is their greatly reduced stability, and relatedly, the low efficiency of refolding the antibodies..." Stayton states further that their research group has "... unexpectedly demonstrated that engineered antibody fragments are not necessarily optimized for folding stability." (*see* Stayton on p. 205, both columns).

Along similar lines, Loboto et al have written about intracellular antibodies and challenges facing their use as therapeutic agents (*see* Lobato et al, Trends in Molecular Med., 9(9): 390-396, 2003). Loboto et al say "... many significant challenges remain to be overcome before intrabodies can be useful therapeutic agents... new developments and advances are needed to allow their efficient delivery and expression for treatment of human diseases." In addition, Loboto et al caution that "Pre-formed antibodies injected into cells do facilitate functional interaction with antigen, but this approach is of limited valued for clinical applications" (*e.g.* requiring sufficient delivery, uptake and stability of intact antibodies). Alternatively, intrabody approaches are being developed, but are far from achieving routine clinical success: "A major challenge for the

successful application of intrabodies for therapy is achieving sufficient internatlization or expression inside target cells." (*see* Lotobo et al at p. 392).

More generally regarding polypeptide delivery to cells, Derossi et al teach the ability of antennapedia homeodomain to translocate through biological membranes, but this ability is highly sequence dependent, and illustrates that delivery of polypeptides to target cells in vitro or in vivo is a rate limiting step for cell targeting and entry for most polypeptides (see D. Derossi et al. J. Biol. Chem. 269(14): 10,444-10,450, especially the abstract on p. 10,444, last paragraph of the introduction on p. 10,444; first full paragraph on p. 10,450: "Other polypeptides that cross biological membranes are those destined, after synthesis, to specific intracellular compartments such as the endoplasmic reticulum or the mitochondria... Passage through these intracellular membranes is energy-dependent and requires the presence of specific proteins that serve as receptors and/or channels. However, even in this rather well studied system, the actual mechanism of importation is not yet completely understood." For specific requirements of other, specialized polypeptides involved in cellular membrane penetration, see M. Pooga et al. FASEB J. 12: 67-77 for a discussion of the remarkable properties of transportan; see also G. Elliott et al, Cell 88 : 223-233 for the distinguishing features of Herpes virus structural protein and its role in intercellular trafficking).

The amount of direction or guidance presented in the specification AND the presence or absence of working examples. The specification teaches the shift in expression of UCP from lysosomes and the mitochondria to the plasma membrane in

MDR cells in vitro. The specification additionally teaches the induction of MDR cell death in vitro comprising the administration of tunicamycin and anti-UCP antibodies. The specification fails to teach a method of regulating lysosomal pH comprising administration of a UCP antibody. One skilled in the art would not accept on its face the examples given in the specification of the changes observed in subcellular expression of UCP in cells in vitro following administration of tunicamycin, or the ability of UCP2 knockout mice to maintain resistance to T. Gondii infection, as being correlative or representative of successfully regulating lysosomal pH following the administration of antibodies. The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with in vivo delivery of UCP antibodies to the lysosome and further whereby lysosomal UCP activity is modified and lysosomal pH is regulated.

The breadth of the claims and the quantity of experimentation required. The claims are drawn to a method for regulating lysosomal pH by modifying lysosomal UCP activity comprising contacting a cell in vitro or in vivo with a lysosomal UCP inhibitor that is a UCP antibody. The quantity of experimentation required to practice the invention as claimed would require the *de novo* identification of an antibody which specifically binds lysosomal UCP and thereby regulated lysosomal pH, as well as determination of appropriate modes of administration of such an antibody whereby the appropriate target cells and suborganelles are targeted with sufficient amounts of functional antibody, and further whereby UCP activity is modified appropriately upon antibody binding and lysosmal pH is appropriately regulated. Since the specification

fails to provide sufficient guidance for the identification of such an antibody, whereby the antibody is adequately delivered to the target cells and appropriate organelles, lysosomal UCP is appropriately modulated and lysosomal pH is appropriately regulated in vivo or in vitro, and since determination of these factors is highly unpredictable, it would require undue experimentation to practice the invention over the scope claimed.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ə 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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